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DECADRON AND OTHER ADRENAL STEROIDS

Dexamethasone (Decadron - Merck Sharp & Dohme) is being offered to the medical profession as "the crowning achievement of the first corticosteroid decade." Experience with this new drug is limited; at this point Decadron appears to be a useful but not remarkable addition to the group of anti-inflammatory steroids that includes cortisone, hydrocortisone, prednisone and prednisolone (Meticorten and Meticortelone - Schering; and other brands), methylprednisolone (Medrol - Upjohn), and triamcinolone (Aristocort - Lederle; and Kenacort - Squibb). Deronil, another brand of dexamethasone, will soon by marketed by Schering.

A given dose of dexamethasone is equivalent therapeutically to a much larger dose of any of the other drugs in the group. But the smaller dosage in itself means practically nothing. The important question is whether the smaller dosage is accompanied, as claimed, by fewer and milder side effects. Evidence up to now indicates side effects with dexamethasone similar to those with other steroids. (See proceedings of conference on "A Decade of Anti-Inflammatory Steroids, from Cortisone to Dexamethasone," Dec. 15-16, 1958, to be published by N. Y. Academy of Sciences.) Reliable knowledge of the frequency and severity of the side effects must await much longer experience with the drug.

CAUTION NEEDED - Almost every new steroid is introduced with the claim that it has fewer or milder side effects, and there are always early clinical impressions to back the claim. Caution is necessary in assessing these early reports, because with the passage of enough time the usual side effects are likely to appear. For example, triamcinolone, especially when used in high dosages, was found after a time to cause peculiar muscle weakness and occasional muscle wasting together with weight loss; and these reactions have apparently occurred in the absence of hypopotassemia.

When prednisone and prednisolone were introduced in 1955, they offered the therapeutic advantages of cortisone and hydrocortisone, but with decreased salt and water retention and with little excretion of potassium. Unlike cortisone and hydrocortisone, they could be taken without risk that they would aggravate hypertension and heart failure. But they showed all the other undesirable properties associated with the carbohydrate-influencing action of cortisone and hydrocortisone. And no steroid yet discovered has anti-inflammatory effects in high degree without at the same time producing serious side effects; all of the anti-inflammatory steroids, including dexamethasone, can cause peptic ulceration, decreased resistance to infection, osteoporosis and pathological fractures, insomnia, rounding of the face, excitability ranging to outright psychoses, and exacerbation of diabetes.

With all of the drugs in the group of newer steroids, sodium retention is not significant; excessive potassium loss at its worst is easily controlled by having the patient take potassium chloride tablets or foods rich in potassium, such as orange or grapefruit juice (about 0.2 Gm. per 4-oz. serving), or bananas (about 0.5 Gm. in an average banana).

CONTRAINDICATIONS - In prescribing any of these drugs, the physician should constantly have in mind the wide range of serious side effects and the conditions in which the use of any adrenal steroid is hazardous. In fact, the contraindications given by Merck in an advertisement for Decadron can properly be applied – as a minimum – to all of the steroids. Merck warns: "Herpes simplex of the eye is an absolute contraindication to corticosteroid therapy. Decadron must be administered with caution in tuberculosis, other acute and chronic infections, peptic ulcer, osteoporosis, fresh intestinal anastomoses, diverticulitis, thrombophlebitis, pregnancy, and in the presence of psychotic tendencies." (The absence of "psychotic tendencies" does not, however, insure against their appearance from steroid therapy.)

Merck's statement that Decadron would cost less than therapeutically equivalent doses of other steroids was not confirmed by a price check of a number of New York drug stores. (The equivalent therapeutic doses of the various preparations, as compared with 25 mg. of cortisone and 20 mg. of hydrocortisone are: prednisone, 5 mg.; prednisolone, 5 mg.; methylprednisolone, 4 mg.; triamcinolone, 4 mg.; and dexamethasone, 0.75 mg.)

BUFFERED TETRACYCLINE AND ANTIBIOTIC BLOOD LEVELS

Physicians have been told repeatedly over the past year that the newer, buffered tetracycline products are vastly superior to the older tetracyclines. The claims of rapid absorption and high antibiotic blood levels have been so impressive that the buffered tetracyclines have almost completely replaced the older tetracyclines in medical practice; more important, the newer tetracyclines have been increasingly – and often mistakenly – used in place of other antibiotics.

Various buffering agents are found in these newer products. They include metaphosphate (in Panmycin KM - Upjohn); citric acid (in Achromycin V - Lederle); glucosamine (in Cosa-Tetracyn - Pfizer); and a tetracycline phosphate complex (in Tetrex - Bristol; Sumycin - Squibb; Panmycin Phosphate - Upjohn; Tetracyn V - Pfizer). The evidence that these agents cause a significant increase in antibiotic blood levels has been confused and contradictory.

EVIDENCE BASED ON ERROR - Much of the evidence was based on sheer error. Tetracycline capsules originally contained as fillers certain calcium salts which actually depressed absorption of the antibiotic. What was taken to be a potentiating effect, in some of the studies, was largely, if not entirely, the result of elimination of the retardant. This error was pointed out a year ago in an editorial in the New England Journal of Medicine. It was pointed out again by Maxwell Finland in the June 1958 issue of Antibiotic Medicine and Clinical Therapy, and even more recently by Charles May in an editorial entitled, "Gilded Antibiotics," in the September 1958 issue of Pediatrics. Nevertheless, claims apparently based on the erroneous comparisons continue to be made.

More recent studies are not subject to criticism on the same ground, but they have been sharply criticized on other grounds. Thus, much of the evidence of higher blood levels has been found to be statistically unsound. Some of the increased blood levels reported have been less than the technical or experimental variations usual in such assays (plus-or-minus 25%). Even in studies showing more significant increases in average antibiotic blood levels, the use of buffered tetracycline resulted in lower levels in many of the subjects than the same doses of plain tetracycline.

CLINICAL SIGNIFICANCE - Despite the confusion of the evidence, somewhat higher antibiotic blood levels may, in fact, result from the addition of the various buffering agents. To the physician, the important thing is that elevations even of the order claimed have no real clinical significance. Because of the great differences in absorption among patients, the recommended doses of antibiotics make allowance for low absorption by some patients. The possibility of a somewhat higher average blood level would not permit a general lowering of the dosage or lengthening of the interval between doses to minimize side effects or to reduce costs. (It is of interest that the pharmaceutical houses recommend the same doses of buffered tetracycline and of plain tetracycline.) If an organism is sensitive to tetracycline, a higher blood level of the order claimed would make no significant difference in the clinical outcome. On the other hand, for a resistant organism, blood levels many times greater than normal would be needed – levels much higher than can be achieved with any tetracycline product now available.

And here we come to the crux of the problem. A large and growing proportion of pathogenic organisms are resistant to tetracycline, buffered or unbuffered. Resistant strains of staphylococci, enterococci, and enteric Gram-negative bacilli (Esch. coli, Aerobacter aerogenes, Proteus, and Pseudomonas aeruginosa) are becoming much more prevalent and more dangerous, largely because of the widespread and often excessive use of tetracyclines. This situation is becoming so serious that tetracycline in any form should be used sparingly; for a large percentage of infections in which it is now used, other antibiotics should be substituted. The overenthusiastic promotion of buffered tetracycline products is regrettable, not because these products have now largely replaced plain tetracycline, but because the promotion has encouraged the excessive use of tetracycline and brought closer the time when this drug will have relatively little usefulness as an anti-infective agent.

MEPROBAMATE

Few drugs in recent times have swept to eminence so quickly as meprobamate (Miltown - Wallace; Equanil - Wyeth). Is its present eminence as a tranquilizer deserved? A recent review from Johns Hopkins of almost a hundred papers on meprobamate (V. G. Laties and B. Weiss, J. Chronic Diseases 7:500, 1958) raises serious doubts.

Meprobamate is most often prescribed for the treatment of anxiety or tension in the patient seen in the doctor's office, and there have been numerous reports of impressive results from such use of the drug. But according to the Johns Hopkins investigators, most of the studies were so poorly conducted that no valid conclusions can be drawn from their data. The few studies that were adequately controlled raise a question as to whether meprobamate in smaller doses has much more effect than a

placebo in relieving anxiety and tension, though the larger doses used with institutionalized patients clearly did have some effect.

Whatever effect meprobamate does have appears to be comparable to that of a hypnotic. In one controlled study by Dr. Louis Lasagna of Johns Hopkins (J. Chronic Diseases 3:122, 1956), doses of 400 to 800 mg. of meprobamate given at bedtime to patients suffering from insomnia proved better than placebos in inducing and maintaining sleep; but meprobamate did not appear significantly different in these respects or in residual sedation from 100 to 200 mg. doses of phenobarbital. These findings have been confirmed by subsequent studies. There is little evidence that the drug is qualitatively different in its clinical effects from a number of other hypnotics including barbiturates, according to Dr. Lasagna. The widely held belief that meprobamate has virtues in relieving anxiety and tension that are unique or different from those of barbiturates does not appear to be justified by available evidence.

SIDE EFFECTS AND ADDICTION - The evidence does not show that meprobamate has fewer side effects than the barbiturates. According to the A.M.A. Council on Drugs (J.A.M.A. 7164:1332, 1957), "Meprobamate is capable of producing a rather wide variety of side-effects and untoward reactions.... Dermal manifestations have included urticaria and diffuse maculopapular and erythematous skin rash, often accompanied by intense pruritus. Shaking chills and fever may also occur. Some patients have experienced these allergic reactions after single oral doses of as little as 0.4 gm." In New and Non-Official Drugs, 1958, the Council warns that the drug should be administered cautiously to allergic patients or those with marked capillary fragility. The available evidence also leaves no doubt that addiction can be induced with meprobamate. As with barbiturates, if a large enough dose is taken over a long enough period and then abruptly stopped, withdrawal symptoms, often including convulsions, will occur.

It may be that the intensive promotion of meprobamate and the publicity it has received in the lay press give it special virtues as a placebo. Apart from placebo effect, however, there is little reason to prescribe meprobamate at 8¢ per 400 mg. tablet in preference to phenobarbital, which is much cheaper. (Meprobamate as a muscle relaxant will be discussed in a future issue.)

NIH 7519 - A NEW ANALGESIC DRUG

The development of a new analgesic drug 10 times as potent as morphine, which "appears to be less addicting and safer than morphine," was announced by Secretary of Health, Education, and Welfare Flemming on Jan. 13. The drug, NIH 7519, was developed at the National Institutes of Health. Information received by The Medical Letter confirms the statement that the new drug is much more potent, mg. for mg., than morphine, making it possible to administer it in smaller doses. The statement concerning safety appears premature. The drug is being tested at the addiction center of the Public Health Service Hospital in Lexington, Ky.; it is not known at this point that it will be less addicting than morphine in equivalent analgesic doses, or that it will have fewer side effects. The National Research Council has recommended that the drug be placed on the narcotics list. According to the National Institutes of Health, it will be at least six months before the drug is marketed.